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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 99N-0188]

Progestational Drug Products for Human Use; Requirements for Labeling Directed to the Patient

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revoke its regulation requiring patient labeling for progestational drug products. This patient labeling is required to inform patients of an increased risk of birth defects reported to be associated with the use of these drugs during the first 4 months of pregnancy. FDA has concluded that, based on a review of the scientific data, such labeling for all progestogens is not warranted. In addition, the diversity of drugs that can be described as progestational, and the diversity of conditions these drugs may be used to treat, make it inappropriate to consider these drugs a single class for labeling purposes. This action is intended to provide consumers with more appropriate labeling for certain drug products.

DATES: Written comments by (*insert date 90 days after date of publication in the Federal Register*). See section VI of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Diane V. Moore, Center for Drug Evaluation and Research (HFD-580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4260.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 22, 1977 (42 FR 37646), FDA published a notice setting forth professional labeling for progestational drug products, other than progestogen-containing products for contraception, and included a box warning recommending against use during the first 4 months of pregnancy. The category “progestational drug products” includes natural progesterone and all synthetic progestins. The basis for the warning, as stated in the notice, was:

Reports during the past several years have indicated that the use of sex hormones during early pregnancy may seriously damage the offspring. Several reports suggest an association between intrauterine exposure to sex hormone treatment and congenital anomalies, including congenital heart defects and limb reduction defects.

Based on these reports, FDA also published in the **Federal Register** of July 22, 1977 (42 FR 37643), a proposed rule to require patient labeling for progestational drug products. The final regulation was published in the **Federal Register** of October 13, 1978 (43 FR 47178), and it is codified at § 310.516 (21 CFR 310.516). It requires that progestational drug products be dispensed with a patient package insert containing a “brief discussion of the nature of the risks of birth defects resulting from the use of these drugs during the first 4 months of pregnancy” (§ 310.516(b)(4)). The regulation applies to any drug product that contains a progestogen, with the exceptions of contraceptives and oral dosage forms labeled solely for the treatment of advanced

cancer¹ (§ 310.516(e)(4)). Texts for patient and professional labeling were published at the same time and contained essentially the same warning concerning heart and limb defects (see 42 FR 37646 at 37647 and 37648, July 22, 1977).

In the late 1980's, FDA evaluated the scientific literature concerning the possible teratogenicity of progestational drugs and concluded that the labeling for progestational drug products should be revised. Available evidence indicated the warning about congenital heart defects and limb reduction defects should be deleted. At that time, several reports suggested an association between exposure to progestational drugs during pregnancy and an increased risk of hypospadias in male fetuses and mild virilization of the external genitalia in female fetuses.

Because FDA continued to believe that there was some risk of birth defects associated with progestogens, the patient labeling and box warning statements were revised. In the **Federal Register** of January 12, 1989 (54 FR 1243), FDA published revised guideline texts for patient and professional labeling for progestational drug products that deleted the warning about possible congenital heart defects and limb reduction defects and added a warning about an increased risk of certain genital abnormalities. The revised patient labeling, which is still in use, is as follows:

Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.

There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8

¹ The original regulation exempted contraceptives, which were required to comply with the labeling requirements of 21 CFR 310.501. In 1981 the regulation was amended to exempt advanced cancer drugs (46 FR 53656, October 30, 1981).

per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.

These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available.

If you take (name of drug) and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

At the time patient labeling was first required for progestational drugs, there was concern that all sex hormones might be teratogenic. This concern was based on a diverse collection of literature reports, including reports on androgens, estrogens, and progestogens, often in combination. It was frequently unclear what drug or combination of drugs the women had taken. In 1976, FDA published the text of patient labeling for estrogens that included a warning about congenital heart defects and limb reduction defects (see 41 FR 43117, September 29, 1976). In the **Federal Register** notice of July 22, 1977 (42 FR 37646 at 37647), setting forth professional labeling for progestational drug products, FDA described the category of “progestational drug products” and noted the need for appropriate warnings for these drugs in the belief that all sex hormones, including all progestogens, had teratogenic potential. The notice listed the following drugs, and their salts and esters, as examples of progestational drugs: Dimethisterone, dydrogesterone, ethinylestrenol, ethynodiol, hydroxyprogesterone, medroxyprogesterone, megestrol, norethindrone, norethynodrel, norgestrel, and progesterone. The notice made clear that this list was nonexhaustive and that the warning would apply to all progestational agents, including drugs later approved. In 1989, when the guideline texts for patient and professional labeling were revised

to warn about hypospadias and virilization of the female genitalia, the warning continued to apply to progestogens as a class.

FDA has recently reviewed the evidence suggesting that progestogen use during pregnancy is associated with an increased risk of genital abnormalities. The notion that progestogens are associated with an increased risk of hypospadias comes from compiling cases from heterogeneous sources, largely case reports. Hypospadias has been reported to be associated with seven progestational agents, although for several of these progestogens, only one case has been reported. The data include cases where women were exposed to other hormones or drugs in addition to progestogens. The reasons for progestogen exposure varied, including: Hormonal pregnancy tests, treatment of threatened or habitual abortion, luteal phase deficiency, and contraception; yet studies often failed to control for the condition being treated. One study included infants who were genetically predisposed to hypospadias (Refs. 1 through 3).

As discussed previously, the warning concerning an association between progestogens and hypospadias was based on heterogeneous sources. Since the early reports suggesting teratogenicity, several progestational agents have been thoroughly investigated. The reliable evidence, particularly from controlled studies, shows no increase in congenital anomalies, including genital abnormalities in male or female infants, from exposure during pregnancy to progesterone (Refs. 4 through 7) or hydroxyprogesterone (Refs. 4 through 7, 9 and 10).

Analysis of the literature associating progestogen use during pregnancy with virilization of the genitalia in female infants indicates that most cases involved high doses of androgen-derived progestins, particularly ethisterone and norethindrone (Refs. 2, 11, and 12). Norethindrone in doses ranging from 10 to 40 milligrams per day (mg/d), and sometimes as much as 120 mg/d, was used in the 1950's and 1960's as a treatment for threatened abortion (Ref. 13). The other drugs that account for most of the recorded cases of female masculinization are methyltestosterone, methandriol, and danazol (Ref. 2).

Thus, there are significant differences among progestational drugs. Accordingly, FDA concludes that, based on a review of the scientific data, a warning of an increased risk of birth defects on all progestogen labeling is not warranted. Class labeling for progestogens is also inappropriate because it applies without regard to the indication for which the drug is prescribed.

At the time patient labeling was first required for progestational drugs, progestogens had been commonly used as hormonal pregnancy tests, as a treatment for habitual or threatened abortion, and for the treatment of secondary amenorrhea and abnormal uterine bleeding. Since that time, some of these uses have been abandoned and new uses have emerged. Hormonal pregnancy tests are no longer available in the United States. Progestational drugs have been labeled as ineffective for the prevention of spontaneous abortion for 20 years.

Medroxyprogesterone in combination with estrogen is now widely prescribed to postmenopausal women for hormone replacement therapy. By definition, postmenopausal women cannot become pregnant, yet the current regulation requires that they receive a warning about use in pregnancy.

The use of progesterone for luteal phase support with in vitro fertilization has become routine. FDA recently approved a progesterone gel for progesterone supplementation or replacement as part of an Assisted Reproductive Technology program for infertile women. The American College of Obstetricians and Gynecologists has objected to the progestational patient labeling requirement as applied to progesterone because “there are no data to indicate that the use of progesterone causes any teratologic effects, and the FDA warning is disturbing to infertility patients taking progesterone.”²

Because of the diversity of the drugs that can be described as progestational, the lack of reliable scientific evidence linking most of these drugs to an increased risk of birth defects, and the diversity of the conditions these drugs may be used to treat, FDA believes it is inappropriate

²Letter from Stanley Zinberg, dated December 31, 1996.

to require that progestational drug products be dispensed with patient labeling that warns of an increased risk of birth defects. Therefore, FDA is proposing to remove this requirement.

For the reasons discussed previously, FDA believes that it is no longer appropriate for professional labeling to contain a box warning recommending against the use of progestational drug products during the first 4 months of pregnancy. There is also no need to contraindicate progestogens as a diagnostic test for pregnancy because hormonal pregnancy tests are no longer available in the United States. In a notice published elsewhere in this issue of the **Federal Register**, FDA is announcing its intent to revoke its previously issued guidance texts for physician and patient labeling for progestational drug products. When this proposed rule concerning patient labeling becomes final, holders of approved applications for progestational drug products will be required to revise the labeling of such products by removing the text for patient labeling. In addition, at that time, holders of approved applications should revise the professional labeling to remove the box warning and the contraindication as a diagnostic test for pregnancy. These labeling revisions will not require a supplemental application, but may be reported in the next annual report, as provided for in 21 CFR 314.70(a) and (d).

II. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Raman-Wilms, L. et al., "Fetal Genital Effects of First-Trimester Sex Hormone Exposure: A Meta-Analysis," *Obstetrics and Gynecology*, 85:141–149, 1995.
2. Schardein, J. L., "Chemically Induced Birth Defects," Marcel Dekker, Inc., New York, 1993.
3. Scialli, A. R., The REPROTOX System, Reproductive Toxicology Center, Washington, DC.
4. Check, J. H. et al., "The Risk of Fetal Anomalies as a Result of Progesterone Therapy During Pregnancy," *Fertility and Sterility*, 45:575–577, 1986.

5. Heinonen, O. P., D. Slone, and S. Shapiro, "Birth Defects and Drugs in Pregnancy," Publishing Sciences Group, Littleton, MA, 1977.
6. Michaelis, J. et al., "Prospective Study of Suspected Associations Between Certain Drugs Administered During Early Pregnancy and Congenital Malformations," *Teratology*, 27:57-64, 1983.
7. Resseguie, L. J. et al., "Congenital Malformations Among Offspring Exposed In Utero to Progestins, Olmsted County, MN," *Fertility and Sterility*, 43:514-519 1985.
8. Rock, J. A. et al., "Fetal Malformations Following Progesterone Therapy During Pregnancy: A Preliminary Report," *Fertility and Sterility*, 44:17-19, 1985.
9. Katz, Z. et al., "Teratogenicity of Progestogens Given During the First Trimester of Pregnancy," *Obstetrics and Gynecology*, 65:775-780, 1985.
10. Varma, T. R., and J. Morsman, "Evaluation of the Use of Proluton-Depot (Hydroxyprogesterone Hexanoate) in Early Pregnancy," *International Journal of Gynaecology and Obstetrics*, 20:13-17, 1982.
11. Wilkins, L., "Masculinization of Female Fetus Due to Use of Orally Given Progestins," *Journal of the American Medical Association*, 172:1028-1032, 1960.
12. Wilson, J. G., and R. L. Brent, "Are Female Sex Hormones Teratogenic?" *American Journal of Obstetrics and Gynecology*, 141:567-580, 1981.
13. Jacobson, B. D., "Hazards of Norethindrone Therapy During Pregnancy," *American Journal of Obstetrics and Gynecology*, 84:962-968, 1962.

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612) and the Unfunded Mandates Reform Act of 1995

(Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant impact on small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities.

The Unfunded Mandates Reform Act of 1995 (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and these two statutes. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant effect on a substantial number of small entities. Because the proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in a 1-year expenditure of \$100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act of 1995.

The proposed rule would remove certain information from the professional labeling of affected drug products. The revised labeling may be filed in the next annual report. The agency has identified 13 sponsors and 16 distinct professional labeling inserts that would need to be changed to comply with this rule. Using a pharmaceutical labeling cost model developed for the agency, the average cost for this labeling change is \$1,317 per insert, assuming a compliance period of 1 year. Applying this cost to the 16 professional labeling inserts results in a one-time cost of compliance of \$21,000. There will also be an additional minor cost of lost inventory. Of the 13 sponsors affected, fewer than 5 would meet the Small Business Administration definition of small. No additional burdens are imposed upon manufacturers.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. The proposal would remove certain information from the labeling of affected drug products. The revised labeling may be filed in the next annual report, which is already required under FDA's regulations and is already approved by the Office of Management and Budget (OMB) as a collection of information, OMB control no. 0910-0001. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

VI. Proposed Effective Date

FDA proposes that any final rule based on this proposal be effective 1 year after its date of publication in the **Federal Register**.

VII. Request for Comments

Interested persons may, on or before (*insert date 90 days after date of publication in the Federal Register*), submit to the Dockets Management Branch (address above) written comments on this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 310

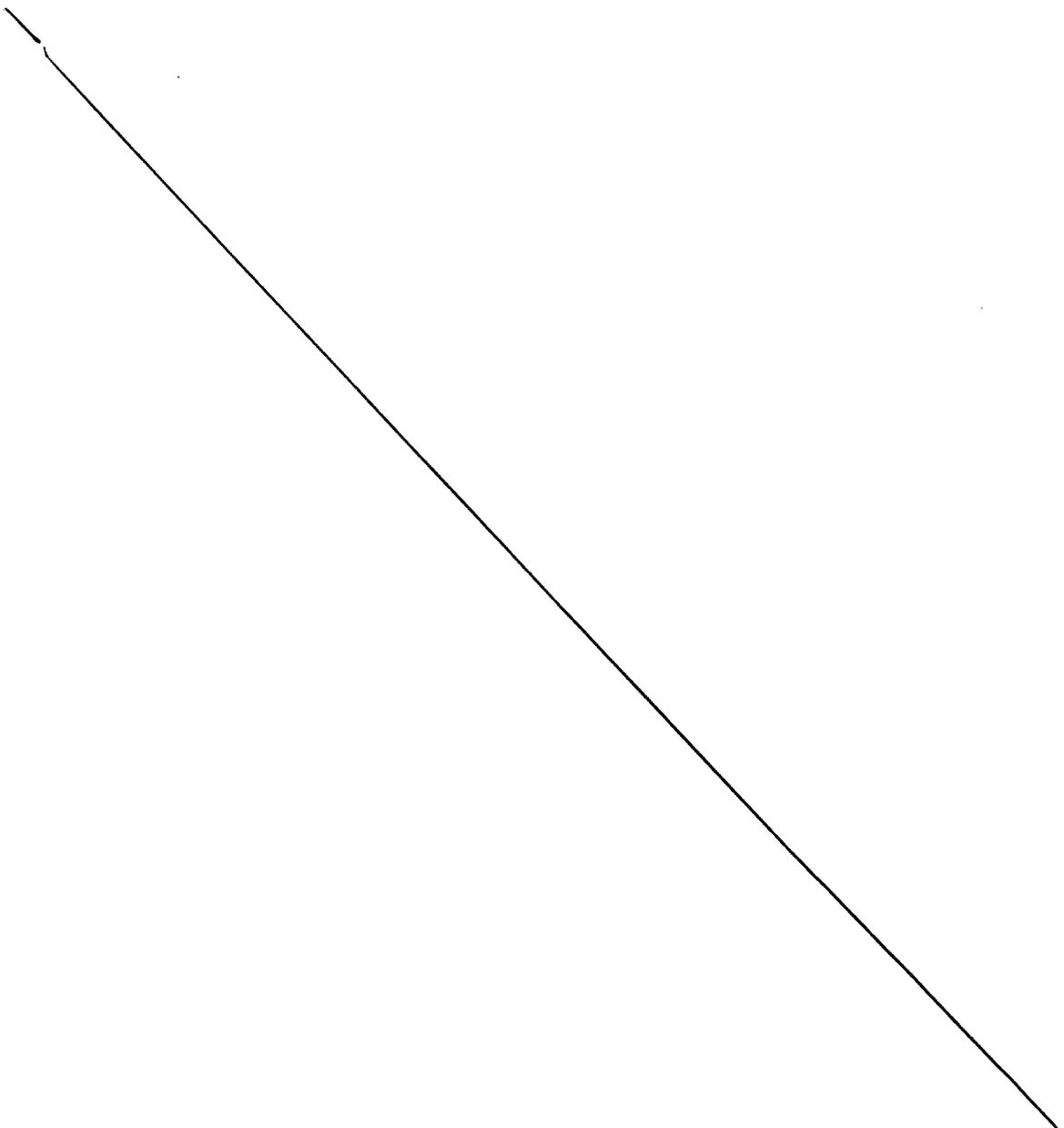
Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 310 be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 360hh–360ss, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.



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§ 310.516 [Removed]

2. Section 310.516 *Progestational drug products; labeling directed to the patient* is removed.

Dated: March 25, 1999
March 25, 1999



William K. Hubbard
Acting Deputy Commissioner for Policy

[FR Doc. 99-???? Filed ??-??-99; 8:45 am]

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